IN THE SPECIFICATION

On page 2, replace the paragraph under the title "Continuing Application Data" with the following:

A1

The instant utility application is based on provisional patent application 60/103,418 filed on October 7, 1998, the entire contents of which is herein incorporated by reference; and, the instant application is related to co-pending utility applications U.S.S.N. 09/375,333 and 09/374,958 (Attorney Docket Nos. STK-075 and STK-076) filed on even date herewith, also based on the aforementioned provisional application, the disclosures of which are herein incorporated by reference.

On page 8, replace the first full paragraph with the following:

A2

Thus, in one aspect, the present invention is directed to a TGF-β superfamily chimeric protein derived from at least two different members of said superfamily, said chimeric protein comprising a dimer wherein one monomer comprises a finger 1 subdomain, a finger 2 subdomain and a heel subdomain, said finger 2 subdomain being derived from a first member of said superfamily, said finger 1 or heel subdomain being derived from a second, different member of said superfamily, wherein said monomer further comprises a conserved C-terminal cysteine skeleton. In a preferred embodiment, the finger 1 or heel subdomain is derived from the BMP-7, OP-1 (SEQ ID NO: 39). In other preferred embodiments, the finger 2 domain is derived from CDMP-2 (SEQ ID NO: 86) or BMP-2 (SEQ ID NO: 49). It is further

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* (...continued)
3, 5 and 7. In that Appendix, the added portion of text is underscored and the deleted portion is bracketed.

A2 cont

contemplated that the chimeras of the instant invention can be homodimeric or heterodimeric.

On page 9, replace the last paragraph with the following:

A3

Modified proteins of the invention can be used in conjunction with a biocompatible matrix such as, but not limited to, collagen, hydroxyapatite, ceramics or carboxymethylcellulose, or other suitable matrix material. Such combinations are particularly useful in methods for regenerating bone, cartilage and/or other non-mineralized skeletal or connective tissues such as but not limited to ligament, tendon, muscle, articular cartilage, fibrocartilage, joint capsule, menisci, intervertebral discs, synovial membrane tissue, and fasica to name but a few. See e.g. U.S. Patent No. 5,496,552, 5,674,292, 5,840,325 and U.S.S.N. 08/253,398, soon-to-issue as U.S. 5,906,827, the disclosures of which are incorporated by reference herein; also incorporated by reference herein are co-pending U.S.S.N. 08/459,129 and 08/458,811 each filed on June 2, 1995. The instant invention contemplates that the binding and/or adherence properties to such matrix materials can be altered using the domain swapping techniques disclosed herein.

On page 13, replace the brief description of figure 1 with the following:

A4

Figure 1 lists the aligned C-terminal residues defining the finger 2 sub-domain for various known members of the BMP family, and TGF-β superfamily of proteins, starting with the first residue following the cysteine doublet. OP-1 (amino acid residues 66-102 of SEQ ID NO: 55); BMP-5 (amino acid residues 66-102 of SEQ ID NO: 52);

BMP-6 (amino acid residues 66-102 of SEQ ID NO: 53); OP-2 (amino acid residues 66-102 of SEQ ID NO: 56); OP-3 (amino acid residues 66-102 of SEQ ID NO: 57); 60A (amino acid residues 82-118 of SEQ ID NO: 48); Vg-1 (amino acid residues 66-102 of SEQ ID NO: 46); Univin (amino acid residues 1-35 of SEQ ID NO: 34); BMP-2 (amino acid residues 66-102 of SEQ ID NO: 49); BMP-4 (amino acid residues 65-101 of SEQ ID NO: 51); GDF-5 (amino acid residues 66-102 of SEQ ID NO: 83); GDF-6 (amino acid residues 66-102 of SEQ ID NO: 85); GDF-7 (amino acid residues 66-102 of SEQ ID NO: 87); CDMP-2 (amino acid residues 66-102 of SEQ ID NO: 86); DPP (amino acid residues 66-102 of SEQ ID NO: 45); BMP-9 (amino acid residues 1-35 of SEQ ID NO: 7); Dorsalin (amino acid residues 66-103 of SEQ ID NO: 54); BMP-10 (amino acid residues 1-35 of SEQ ID NO: 8); GDF-3 (amino acid residues 65-101 of SEQ ID NO: 59); GDF-1 (amino acid residues 71-107 of SEQ ID NO: 58); SCREW (amino acid residues 1-35 of SEQ ID NO: 28); BMP-3 (amino acid residues 67-103 of SEQ ID NO: 50); NODAL (amino acid residues 1-34 of SEQ ID NO: 25); TGF-β1 (amino acid residues 63-98 of SEQ ID NO: 40); TGF-β2 (amino acid residues 63-98 of SEQ ID NO: 41); TGF-β3 (amino acid residues 63-98 of SEQ ID NO: 42); TGF-β4 (amino acid residues 63-98 of SEQ ID NO: 43); TGF-β5 (amino acid residues 63-98 of SEQ ID NO: 44); GDF-5 (amino acid residues 63-98 of SEQ ID NO: 40); Inhibin α (amino acid residues 66-105 of SEQ ID NO: 61); Inhibin βA (amino acid residues 70-106 of SEQ ID NO: 62); Inhibin βB (amino acid residues 70-106 of SEQ ID NO: 63); Inhibin βC (amino acid residues 1-35 of SEQ ID NO: 23); MIS (amino acid residues 1-34 of SEQ ID NO: 24); GDNF (amino acid residues 1-32 of SEQ ID NO: 19); BMP-11 (amino acid residues 1-35 of SEQ ID NO: 9); GDF-9 (amino acid residues 66-102 of SEQ ID NO: 60).

A4 cont.

On page 13, replace the brief description of figure 3 with the following:

AS

Figure 3 is a nucleotide sequence and the corresponding amino acid sequence of the OP-1 C-terminal seven cysteine active domain. The DNA sequence corresponds to nucleotides 1036-1341 of SEQ ID NO: 38. The protein sequence corresponds to amino acid residues 330-431 of SEQ ID NO: 39.

On pages 13-14, replace the brief description of figure 6 with the following:

A6

Figures 6A, 6B, and 6C are sequence alignments using single letter amino acid code, arranged to indicate homologies of the finger 1, heel, and finger 2 regions, respectively, of some known members of the TGF-β superfamily. Shown are the respective amino acids comprising each region of human TGF-β1 through TGF-β5 (the TGF-β subgroup), the Vg/dpp subgroup consisting of dpp, Vg-1, Vgr-1, 60A (see copending U.S.S.N. 08/271,556), BMP-2A (also known in the literature as BMP-2), dorsalin, BMP-2B (also known in the literature as BMP-4), BMP-3, BMP-5, BMP-6, OP-1 (also known in the literature as BMP-7), OP-2 (see PCT/US91/07635 and U.S. Patent No. 5,266,683) and OP-3 (U.S.S.N 07/971,091), the GDF subgroup consisting of GDF-1, GDF-3, and GDF-9, the Inhibin subgroup consisting of Inhibin α, Inhibin βA, and Inhibin βB. The dashes (-) indicate a peptide bond between adjacent amino acids. A consensus sequence pattern for each subgroup is shown at the bottom of each subgroup. In Figure 6A the finger 1 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 1-34 of SEQ ID NO:40); TGF-β2 (residues 1-34 of SEQ ID NO:41); TGF-β3 (residues 1-34 of SEQ ID NO:42); TGF-β4 (residues 1-34 of SEQ ID NO:43); TGF-β5 (residues 1-34 of SEQ ID NO:44);

TGF-β pattern (1-34 of SEQ ID NO: 64); dpp (residues 1-34 of SEQ ID NO:45); Vg-1 (residues 1-34 of SEQ ID NO:46); Vgr-1 (residues 1-34 of SEQ ID NO:47); 60A (residues 1-34 of SEQ ID NO:48); BMP-2A (residues 1-34 of SEQ ID NO:49); DORSALIN (residues 1-34 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 1-34 of SEQ ID NO: 51); BMP-3 (residues 1-34 of SEQ ID NO: 50); BMP-5 (residues 1-34 of SEQ ID NO:52); BMP-6 (residues 1-34 of SEQ ID NO:53); OP-1/BMP-7 (residues 1-34 of SEQ ID NO:55); OP-2 (residues 1-34 of SEQ ID NO:56); OP-3 (residues 1-34 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 1-34 of SEQ ID NO:65); GDF-1 (residues 1-34 of SEQ ID NO:58); GDF-3 (residues 1-34 of SEQ ID NO:59); GDF-9 (residues 1-34 of SEQ ID NO:60); GDF subgroup pattern (residues 1-34 of SEQ ID NO:66); Inhibin α (residues 1-34 of SEQ ID NO:61); Inhibin βA (residues 1-34 of SEQ ID NO:62); Inhibin βB (residues 1-34 of SEQ ID NO:63); Inhibin subgroup pattern (residues 1-34 of SEQ ID NO:67).

AG cont

In Figure 6B the heel sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 35-64 of SEQ ID NO:40); TGF-β2 (residues 35-64 of SEQ ID NO:41); TGF-β3 (residues 35-64 of SEQ ID NO:42); TGF-β4 (residues 35-64 of SEQ ID NO:43); TGF-β5 (residues 35-64 of SEQ ID NO:44); TGF-β pattern (residues 35-64 of SEQ ID NO: 64); dpp (residues 35-67 of SEQ ID NO:45); Vg-1 (residues 35-67 of SEQ ID NO:46); Vgr-1 (residues 35-67 of SEQ ID NO:47); 60A (residues 35-67 of SEQ ID NO:48); BMP-2A (residues 35-66 of SEQ ID NO:49); DORSALIN (residues 35-67 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 35-66 of SEQ ID NO: 51); BMP-3 (residues 35-68 of SEQ ID NO: 50); BMP-5 (residues 35-67 of SEQ ID NO:52); BMP-6 (residues 35-67 of SEQ ID NO:53); OP-1/BMP-7 (residues 35-67 of SEQ ID 35-67 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 35-68 of SEQ ID NO:65); GDF-1 (residues 35-72 of SEQ ID NO:58); GDF-3 (residues 35-

66 of SEQ ID NO:59); GDF-9 (residues 35-67 of SEQ ID NO:60); GDF subgroup pattern (residues 35-72 of SEQ ID NO:66); Inhibin α (residues 35-67 of SEQ ID NO:61); Inhibin βA (residues 35-71 of SEQ ID NO:62); Inhibin βB (residues 35-71 of SEQ ID NO:63); Inhibin subgroup pattern (residues 35-71 of SEQ ID NO:67).

A6 cont.

In Figure 6C the finger 2 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 65-98 of SEQ ID NO:40); TGF-β2 (residues 65-98 of SEQ ID NO:41); TGF-β3 (residues 65-98 of SEQ ID NO:42); TGF-β4 (residues 65-98 of SEQ ID NO:43); TGF-β5 (residues 65-98 of SEQ ID NO:44); TGF-β pattern (residues 65-98 of SEQ ID NO: 64); dpp (residues 68-102 of SEQ ID NO:45); Vg-1 (residues 68-102 of SEQ ID NO:46); Vgr-1 (residues 68-102 of SEQ ID NO:47); 60A (residues 68-102 of SEQ ID NO:48); BMP-2A (residues 68-102 of SEQ ID NO:49); DORSALIN (residues 68-103 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 68-102 of SEQ ID NO: 51); BMP-3 (residues 68-102 of SEQ ID NO: 50); BMP-5 (residues 68-102 of SEQ ID NO:52); BMP-6 (residues 68-102 of SEQ ID NO:53); OP-1/BMP-7 (residues 68-102 of SEQ ID NO:55); OP-2 (residues 68-102 of SEQ ID NO:56); OP-3 (residues 68-102 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 68-103 of SEQ ID NO:65); GDF-1 (residues 73-107 of SEQ ID NO:58); GDF-3 (residues 67-101 of SEQ ID NO:59); GDF-9 (residues 68-102 of SEQ ID NO:60); GDF subgroup pattern (residues 73-107 of SEQ ID NO:66); Inhibin α (residues 68-105 of SEQ ID NO:61); Inhibin βA (residues 72-106 of SEQ ID NO:62); Inhibin βB (residues 72-106 of SEQ ID NO:63); Inhibin subgroup pattern (residues 72-109 of SEQ ID NO:67).

On page 14, replace the brief description of figure 7 with the following:

Figure 7 is a single letter code listing of amino acid sequences, identified in capital letter in standard single letter amino acid code, and in lower case letters to identify groups of amino acids useful in that location, wherein the lower case letters stand for the amino acids indicated in accordance with the pattern definition key table set forth in Figure 8. Figure 7 identifies preferred pattern sequences for constituting the finger 1, heel, and finger 2 regions of biosynthetic constructs of the invention. The dashes (-) indicate a peptide bond between adjacent amino acids. The SEQ ID NOS for the subgroup patterns are as follows: TGF-β subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:64); TGF-β subgroup pattern heel (residues 35-64 of SEQ ID NO:64); TGF-β subgroup pattern finger 2 (residues 65-98 of SEQ ID NO:64); Vg/dpp subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:65); Vg/dpp subgroup pattern heel (residues 35-68 of SEQ ID NO:65); Vg/dpp subgroup pattern finger 2 (residues 69-104 of SEQ ID NO:65); GDF subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:66); GFD subgroup pattern heel (residues 35-72 of SEQ ID NO:66); GDF subgroup pattern finger 2 (residues 73-107 of SEQ ID NO:66); Inhibin subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:67); Inhibin subgroup pattern heel (residues 35-71 of SEQ ID NO:67); Inhibin subgroup pattern finger 2 (residues 72-109 of SEQ ID NO:67).

A7

On page 19, replace the second full paragraph with the following:

A8

As used herein, the "base" or "neck" region of the finger 2 sub-domain is defined by residues 1-10 and 22-31, as exemplified by OP-1 (residues 67-77 and 89 to 98 of SEQ ID NO:55), and counting from the first residue following the cysteine doublet in the C-terminal active domain. (See Fig.

1). As is readily apparent from a sequence alignment of other TGF-β superfamily protein members with OP-1, the corresponding base or neck region for a longer protein, such as BMP-9 or Dorsalin, is defined by residues 1-10 and 23-32 (residues 67-77 and 90-99 of SEQ ID NO:54); for a shorter protein, such as NODAL, the corresponding region is defined by residues 1-10 and 22-30 (amino acid residues 1-10 and 22-30 or SEQ ID NO: 25) (See Fig. 1). In SEQ ID NO: 39, (human OP-1), the residues corresponding to the base or neck region of the finger 2 subdomain are residues 397-406 (corresponding to residues 1-10 in Fig. 1) and residues 418-427 (corresponding to residues 22-31 in Fig. 1).

A8 cont.

On page 31, replace the first full paragraph with the following:

Amino acid sequence patterns showing amino acids preferred at each location in the finger and heel regions, deduced in accordance with the principles described in Smith et al. (1990) supra, also are show in Figs. 6-7, and are referred to as the: TGF-β (SEQ ID NO: 64); Vg/dpp (SEQ ID NO: 65); GDF (SEQ ID NO: 66); and Inhibin (SEQ ID NO: 67) subgroup patterns. The amino acid sequences defining the finger 1, heel and finger 2 sequence patterns of each subgroup are set forth in Figs. 6A, 6B, and 6C, respectively. In addition, the amino acid sequences defining the entire TGF-b, Vg/dpp, GDF and Inhibin subgroup patterns are set forth in the Sequence Listing as SEQ. ID. Nos. 64, 65, 66, and 67, respectively.

A9

IN THE CLAIMS

Please cancel claims 4 and 8-17 without prejudice.

Please amend the claims as follows: